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CLINICAL INVESTIGATIONS

Rate pressure product and the components of heart rate and systolic blood pressure in hospitalized heart failure patients with preserved ejection fraction: Insights from ASCEND-HF

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Background: Heart rate and systolic blood pressure (SBP) are prognostic markers in heart failure (HF) with reduced ejection fraction (HFrEF). Their combination in rate pressure product (RPP) as well as their role in heart failure with preserved ejection fraction (HFpEF) remains unclear.

Hypothesis: RPP and its components are associated with HFpEF outcomes.

Methods: We performed an analysis of Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure (ASCEND-HF; http://www.clinicaltrials.gov NCT00475852), which studied 7141 patients with acute HF. HFpEF was defined as left ventricular ejection fraction ≥40%. Outcomes were assessed by baseline heart rate, SBP, and RPP, as well as the change of these variables using adjusted Cox models.

Results: After multivariable adjustment, in-hospital change but not baseline heart rate, SBP, and RPP were associated with 30-day mortality/HF hospitalization (hazard ratio [HR]: 1.17 per 5-bpm heart rate, HR: 1.20 per 10-mm Hg SBP, and HR: 1.02 per 100 bpm × mm Hg RPP; all $P < 0.05$). Baseline SBP was associated with 180-day mortality (HR: 0.88 per 10-mm Hg, $P = 0.028$). Though change in RPP was associated with 30-day mortality/HF hospitalization, the RPP baseline variable did not provide additional associative information with regard to outcomes when compared with assessment of baseline heart rate and SBP variables alone.

Conclusions: An increase in heart rate and SBP from baseline to discharge was associated with increased 30-day mortality/HF hospitalization in HFpEF patients with acute exacerbation. These findings suggest value in monitoring the trend of vital signs during HFpEF hospitalization.

KEYWORDS

Blood Pressure Control and Regulation, Clinical Trials, Heart Failure

1 | INTRODUCTION

Heart failure (HF) affects >5.5 million people in the United States, with 870 000 individuals diagnosed each year.[1] Although patients with heart failure with preserved ejection fraction (HFpEF) have similar symptoms as patients who have heart failure with reduced ejection fraction (HFrEF), there are clear distinctions from patients with HFrEF, as evidenced by an association with older age and increased comorbidity burden and a lack of medical therapies that improve clinical outcomes in HFpEF.[2–4]

Several studies have established that baseline heart rate is elevated in patients with HF. Many of these studies, however, investigated HFrEF or did not distinguish HFpEF from HFrEF. In an analysis of patients with HFrEF hospitalized for HF, heart rate > 70 bpm was

predictive of post-discharge mortality.[5] Studies have also shown improvement in mortality, morbidity, exercise tolerance, quality of life, and left ventricular ejection fraction (LVEF) in ambulatory patients with HF when heart rate was reduced with β-blockade.[6–11] Furthermore, underlying elevation in systolic blood pressure (SBP) is common in patients with HFpEF. Acute hypertensive episodes may also cause HF exacerbations and are typically a modifiable and treatable condition in these individuals.[12]

Both heart rate and blood pressure are incorporated in the rate pressure product (RPP), an indirect index of myocardial oxygen consumption that predicts cardiac function, morbidity, and mortality in patients with cardiovascular disease. Myocardial oxygen consumption can be assessed in HF patients via invasive hemodynamic monitoring with right-heart catheterization and/or pulmonary artery catheterization.[13–15] However, the simple measure of RPP may provide useful information in a noninvasive manner to risk-stratify and offer prognostic information for patients.[16]

The goal of this study was to examine heart rate, SBP, and RPP in hospitalized patients with HFpEF enrolled in the Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure (ASCEND-HF) trial to better understand how these factors at baseline and their change over time may be associated with clinical outcomes.

2 | METHODS

Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF; http://www.clinicaltrials.gov NCT00476852) was a randomized controlled trial that investigated nesiritide vs placebo in patients hospitalized for acute decompensated HF regardless of LVEF. The design, rationale, and primary results have been published.[17,18] The study enrolled 7141 patients between May 2007 and August 2010 at 398 centers across the world, with institutional review board or ethics approval obtained at each study site and all patients providing informed consent for participation.

LVEF was obtained from case-report forms for participants; the timing and method by which LVEF was ascertained were site-specific and not based on trial protocol. Patients without LVEF measurement were excluded from this analysis. Given the American College of Cardiology/American Heart Association (ACC/AHA) definition of HFrEF as LVEF <40%, variable definitions of HFrEF and HFpEF in the literature, and prior study of LVEF in ASCEND-HF that suggested similar baseline features of LVEF 40% to 50% to those with LVEF >50%, HFpEF included all patients with LVEF ≥40% and HFrEF included those with LVEF <40%.[19]

Vital signs, including heart rate and blood pressure, were measured at multiple time points per trial protocol. Baseline heart rate and SBP were defined as measurements taken at the time of randomization. Discharge heart rate and SBP were defined as measurements taken at the time of discharge or day 10, whichever came first. Change in heart rate and SBP was the absolute difference between measurement at discharge and baseline. RPP was calculated by multiplying heart rate and SBP.

2.1 | Statistical analysis

Baseline patient characteristics were reported for HFpEF patients based on heart rate and SBP dichotomized at the median split for each variable and compared using Pearson χ^2 tests or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The survival distributions between groups were compared using Kaplan–Meier event curves with log-rank test.

The primary outcome of interest was the composite endpoint of 30 day all-cause mortality and rehospitalization for HF; the secondary outcome of interest was all-cause mortality at 180 days. Endpoints were redefined to start from the time of hospital discharge or at 10 days from randomization, whichever came first. Thus patients who died from the time of randomization to discharge or at 10 days were not included in this analysis. The relationship between baseline heart rate (as a continuous variable) and outcomes was evaluated using Cox proportional hazards regression in HFpEF patients. Models were adjusted based on variables consistently used in ASCEND-HF post-hoc analyses that included age, blood urea nitrogen, baseline sodium, and baseline dyspnea.[20,21] Additional adjustment was made with regard to variables that were thought to potentially confound outcome associations in the present analysis: randomization to nesiritide, use of β-blocker, use of calcium channel blocker, implantable cardioverter-defibrillator, and presence of pacemaker. Among patients discharged alive, we evaluated the association between in-hospital change in heart rate and outcomes using Cox models, adjusted for baseline heart rate and an indicator for length of stay >10 days. This analysis was repeated for HFrEF patients. Further, to assess whether the associations between heart rate and outcomes were similar for HFpEF and HFrEF patients, we modeled the interaction of heart rate and HFpEF/HFrEF status in Cox models. Analyses were repeated in a similar way for SBP and RPP.

Proportional hazards and linearity assumptions were assessed for the primary exposure variables and adjustment covariates. No violations were identified for heart rate, SBP, or RPP, and transformations for adjustment covariates were made when appropriate. Multiple imputation with 25 imputations was used for missing data; final results reflect the combined result across all imputations accounting for variation due to missing data. A P value <0.05 was considered significant. Given the exploratory nature of this analysis, there was no adjustment for multiple comparisons. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

Of the 7007 patients enrolled in the ASCEND-HF trial with measured LVEF, 737 (10.5%) had HFpEF. Patient characteristics according to heart rate and SBP are presented in Table 1. Patients with lower heart rate had more comorbidities, including hypertension (HTN), diabetes, COPD, and coronary artery disease, and were more likely to be taking β-blockers or calcium channel blockers at baseline in addition to having a pacemaker compared with patients with higher heart rates. Patients with lower SBP were on similar medical therapy compared

TABLE 1 Baseline characteristics by heart rate and SBP in patients with HFpEF

	Heart Rate, bpm		SBP, mm Hg	
Patient Characteristics	**≤75, N = 370**	**>75, N = 367**	**≤130, N = 393**	**>130, N = 344**
Mean age, y	75 (67–82)[a]	72 (61–80)[a]	75 (67–81)[a]	72 (62–81)[a]
Female sex	49.2	48.2	49.6	47.7
Race				
White	73.2	67.8	72.0	68.9
Black	15.1	18.3	14.5	19.2
Asian	8.6	12.3	11.2	9.6
Other	3.0	1.6	2.3	2.3
BMI, kg/m^2	29 (26–34)	29 (25–34)	29 (25–32)[a]	30 (26–35)[a]
Medical history				
HTN	89.5[a]	82.8[a]	81.4[a]	91.6[a]
DM	53.5[a]	46.3[a]	45.8[a]	54.7[a]
AF/flutter	48.6	52.0	54.7[a]	45.3[a]
COPD	29.7[a]	20.7[a]	28.5[a]	21.5[a]
CAD	67.3[a]	57.8[a]	63.6	61.3
Laboratory values				
Na, mmol/L	140 (137–142)	139 (137–141)	139 (136–141)[a]	140 (137–142)[a]
Cr, mg/dL	1.3 (1.0–1.7)	1.2 (1.0–1.5)	1.3 (1.0–1.6)	1.2 (1.0–1.7)
Hb, g/dL	11.9 (10.6–13.4)	12.2 (11.0–13.7)	12.2 (10.9–13.6)	12.0 (10.8–13.3)
NT-proBNP, pg/mL	3184 (1633–7154)	4339 (2078–7833)	3727 (2128–8117)	3675 (1612–6381)
Medications and devices				
β-Blocker	73.8[a]	61.9[a]	65.1	70.9
ACEI/ARB	60.8	62.1	59.8	63.4
Aldosterone antagonist	16.5	16.3	19.1[a]	13.4[a]
CCB	30.3[a]	21.0[a]	24.4	27.0
Digoxin	11.6	14.4	14.0	11.9
Nitrate	29.2[a]	18.8[a]	22.1	26.2
ICD	6.2	6.3	6.4	6.1
Biventricular pacemaker	5.1	3.0	3.8	4.4
Pacemaker	20.0[a]	8.4[a]	17.8[a]	10.2[a]
HF history				
LVEF, %	50 (45–60)	50 (43–55)	50 (45–60)	50 (44–60)
NYHA class				
I	3.7	9.4	7.2	5.8
II	31.6	22.7	28.7	25.3
III	41.9	26.4	43.3	45.1
IV	22.8	21.6	20.8	23.7
Ischemic etiology	68.9[a]	60.2[a]	65.6	63.4

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; Hb, hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; Na, sodium; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure. Data are presented as % of N or median (IQR).

[a] Indicates $P < 0.05$ for comparison.

with those with higher SBP, with the exception of aldosterone antagonists, which were more common in the lower-SBP group.

Table 2 presents unadjusted and adjusted clinical outcomes in HFpEF. There were 79 deaths or HF rehospitalizations at 30 days and 85 deaths at 180 days. Baseline heart rate and RPP were not associated with primary or secondary outcomes after multivariable adjustment. Baseline SBP was associated with 180-day all-cause mortality in both unadjusted and adjusted Cox models and is further demonstrated in the Figure 1. Changes in heart rate, SBP, and RPP from baseline to discharge were each associated with significant increases in 30-day mortality and HF rehospitalization in both unadjusted and adjusted models, but none of the variables looking at in-hospital change were associated with 180-day all-cause mortality.

Similar analyses were performed in patients with HFrEF (Table 3). There were 247 deaths or HF rehospitalizations at 30 days and 316 deaths at 180 days. In these patients, higher baseline heart rate

TABLE 2 Clinical outcomes in HFpEF by baseline and change in heart rate and SBP

Outcomes	Heart Rate				SBP				RPP			
	Baseline[a]		Change[b]		Baseline[a]		Change[b]		Baseline[a]		Change[b]	
	HR[c] (95% CI)	*P* Value	HR[c] (95% CI)	*P* Value	HR[d] (95% CI)	*P* Value	HR[d] (95% CI)	*P* Value	HR[e] (95% CI)	*P* Value	HR[e] (95% CI)	*P* Value
30-day death or HF rehospitalization												
Unadjusted	0.98 (0.92–1.05)	0.58	1.15 (1.03–1.28)	0.012	0.95 (0.85–1.06)	0.32	1.19 (1.04–1.35)	0.012	1.00 (0.99–1.00)	0.33	1.02 (1.01–1.04)	<0.001
Adjusted[a]	1.00 (0.93–1.07)	0.98	1.17 (1.05–1.31)	0.005	0.99 (0.89–1.10)	0.84	1.20 (1.05–1.37)	0.009	1.00 (0.99–1.01)	0.95	1.02 (1.01–1.04)	<0.001
180-day all-cause mortality												
Unadjusted	1.00 (0.94–1.06)	0.96	0.96 (0.86–1.06)	0.41	0.83 (0.74–0.92)	<0.001	1.02 (0.89–1.16)	0.81	0.99 (0.98–1.00)	0.042	1.00 (0.99–1.01)	0.72
Adjusted[a]	1.02 (0.96–1.09)	0.56	0.97 (0.88–1.08)	0.58	0.88 (0.78–0.99)	0.028	1.07 (0.93–1.22)	0.36	1.00 (0.99–1.01)	0.39	1.00 (0.99–1.01)	0.73

Abbreviations: BUN, blood urea nitrogen; CCB, calcium channel blocker; CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LOS, length of stay; Na, sodium; RPP, rate pressure product; SBP, systolic blood pressure.

[a] Adjusted for age, BUN, baseline Na, baseline dyspnea, randomization to nesiritide, β-blockers, CCB, pacemaker, and ICD. N = 79 for 30-day outcomes; N = 85 for 180-day outcomes.

[b] Adjusted for above variables, plus baseline laboratory values (either heart rate, or SBP or RPP) and an indicator for LOS >10 days. N = 66 for 30-day outcomes; N = 75 for 180-day outcomes.

[c] Per 5-bpm increase.

[d] Per 10-mm Hg increase.

[e] Per 100 bpm × mm Hg increase.

was associated with increased 180-day all-cause mortality in adjusted models. Further, higher baseline SBP was associated with significantly reduced 30-day death or HF rehospitalization and 180-day all-cause mortality. Increase in heart rate from baseline to discharge was also associated with increased 30-day death or HF rehospitalization and 180-day all-cause mortality. Change in SBP from baseline to discharge was not associated with the primary outcome but was associated with 180-day all-cause mortality. Change in RPP from baseline to discharge was associated with a modest increase in 30-day mortality and HF rehospitalization.

Interaction analyses comparing HFpEF and HFrEF populations were not significant for baseline heart rate, SBP, RPP, or the change in any variable with regard to both the primary and secondary outcomes (all $P > 0.05$).

4 | DISCUSSION

In the present analysis, we assessed the association of baseline heart rate, SBP, and RPP in HFpEF patients with acute exacerbation as well as associations between in-hospital changes in these values and post-discharge outcomes. We found that in-hospital changes in each of these parameters were associated with short-term clinical outcomes (30-day mortality or HF hospitalization) in HFpEF, but that only baseline SBP was associated with 180-day mortality in HFpEF. There was also insufficient evidence to support an interaction between these variables and outcome associations based on LVEF.

We found that an increase in SBP and/or heart rate from baseline to discharge in patients with HFpEF was associated with worse outcomes—this in contrast to our findings of higher baseline SBP being associated with lower 180-day all-cause mortality and no association of baseline heart rate with outcomes. An elevated baseline SBP could precipitate an acute HF exacerbation and effectively be treated with medications, leading to improved outcomes. However, when SBP increases during hospitalization, this may be an indicator of uncontrolled HTN or HTN refractory to standard medical therapy.

Indeed, antihypertensive therapy is a key component to managing HF and also to preventing HFpEF.[19] Long-standing HTN increases left ventricular (LV) mass, causing an inability to appropriately fill the LV and maintain cardiac output. Antihypertensive agents have been shown to reduce LV mass and the development of HFpEF.[22–24] The landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study included 404 patients with HFpEF and showed reduced rates of HFpEF in patients on chlorthalidone and a reduced risk for HF hospitalization.[25] Although there are several studies demonstrating improvement in symptoms with blood-pressure reduction in acute HF patients with HTN, the impact of blood-pressure control in the acute setting on clinical outcomes and in the HFpEF population in particular has not been well studied.[26,27]

In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study, re-analysis of the data in the Americas alone showed no significant relationship between SBP and outcomes, suggesting the beneficial effects of spironolactone were independent of blood-pressure effects.[28] However, this was notably in a patient population with better blood-pressure

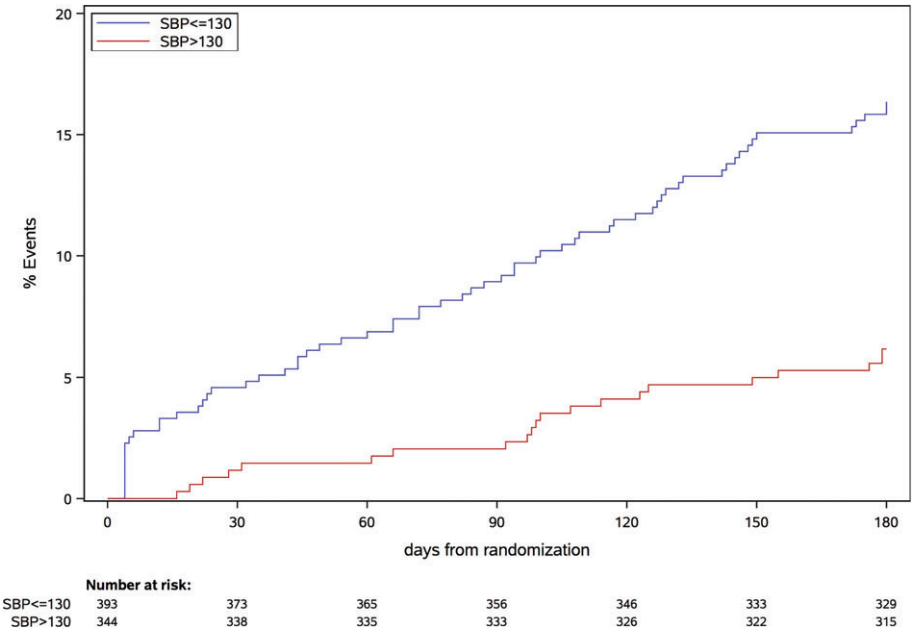

FIGURE 1 Kaplan–Meier event curve for 180-day all-cause mortality in HFpEF patients by baseline SBP, with number at risk at 30-day intervals from randomization by SBP. Abbreviations: HFpEF, heart failure with preserved ejection fraction; SBP, systolic blood pressure

control and thus further reduction of already-controlled blood pressure may not show additional benefit in patients with HFpEF.

A few recent studies have also examined the impact of low SBP in HF. In a retrospective analysis of ASCEND-HF, patients who experienced an episode of hypotension during acute decompensated HF admission had an associated higher 30-day mortality compared with those without a hypotensive episode.[29] Although this analysis did not specifically look at HFpEF patients, it included this cohort, which appears to have similar event rates of hypotension during hospitalization to those with HFrEF, suggesting that in addition to increase in blood pressure during hospitalization, perhaps a decrease in blood pressure—if only transiently—to a hypotensive state may also be detrimental. In an observational study of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF), a registry of patients hospitalized with HF that has been linked with Medicare, the association of the change SBP by 20 mm Hg from admission to discharge as well as discharge SBP was assessed.[30] Change (increase or decrease) in SBP and discharge SBP <120 mm Hg were associated with increased all-cause mortality.[30] Our data support that an increase in SBP is associated with worse outcomes; however, there are key differences in the studies, including HFpEF definitions and outcomes assessed, in addition to the assessment of change in SBP. Overall, our data are consistent with current literature suggesting that there is a range of SBP that may be associated with differential outcomes for HFpEF patients presenting with decompensated HF and the optimal target SBP needs to be better studied and defined.

With regard to heart rate changes during hospitalization, increases in heart rate to initially maintain cardiac output also limit LV filling time, which can reduce output over time and lead to worse outcomes. β-Blocker therapy has been recommended in the latter scenario for controlling heart rate in HF patients.[19] Because β-blockers also affect blood pressure, the broad utility of β-blockers in HFpEF has not been clearly established.[31] And, with conflicting evidence with regard to ivabradine in patients with HFpEF, it is unclear if heart-rate reduction or other processes such as remodeling and improvement in LVEF are the mechanism for potential benefits with this therapy.[32–34] Further complicating the issue of heart rate in HFpEF is chronotropic incompetence, or an abnormal response in heart rate during peak dynamic exercise, which itself predicts mortality.[35,36] In studies of HFpEF patients, even in those not diagnosed with chronotropic incompetence by clinical criteria, heart rate does not augment appropriately with exercise or recover postexercise as compared with controls, suggesting potential autonomic dysregulation.[37]

In another post-hoc analysis of the TOPCAT trial, temporal changes in heart rate during the trial were found to be independent predictors of the composite endpoint of cardiovascular death, aborted cardiac arrest, or HF hospitalization, with increase in heart rate over time associated with higher risk.[38] Although this study was in the outpatient setting of chronic HFpEF patients, an analysis of patients with HFpEF from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry of acute HF used propensity scores to match patients with discharge heart rate < or ≥ 70 bpm.[39] Lower heart rate was associated with lower all-cause mortality in addition to the composite outcome of HF rehospitalization and all-cause mortality during a median follow-up of 2.8 years.[39] Although these studies have some notable differences as previously described, they overall support our data that an elevated heart rate is not favorable and suggests that there may be an element of chronotropic pathology that warrants further study.

In contrast to HFpEF, in patients with HFrEF, both baseline SBP and heart rate were associated with clinical outcomes at 180 days, and heart rate increases from baseline to discharge were associated with worse outcomes at 30 and 180 days. Thus, our data suggest that rising heart rate during hospitalization, regardless of LVEF, portends worse outcomes. In addition, higher SBP in HFrEF, similar to that of

TABLE 3 Clinical outcomes in HFrEF by baseline and change in heart rate and SBP

	Heart Rate				SBP				RPP			
	Baseline[a]		Change[b]		Baseline[a]		Change[b]		Baseline[a]		Change[b]	
Outcomes	HR[c] (95% CI)	*P* Value	HR[c] (95% CI)	*P* Value	HR[d] (95% CI)	*P* Value	HR[d] (95% CI)	*P* Value	HR[e] (95% CI)	*P* Value	HR[e] (95% CI)	*P* Value
30-day death or HF rehospitalization												
Unadjusted	0.99 (0.95–1.03)	0.59	1.12 (1.05–1.19)	<0.001	0.86 (0.80–0.93)	<0.001	1.05 (0.95–1.15)	0.35	0.99 (0.99–1.00)	0.005	1.01 (1.00–1.02)	0.004
Adjusted[a]	1.01 (0.97–1.06)	0.49	1.13 (1.06–1.20)	<0.001	0.89 (0.82–0.96)	0.002	1.06 (0.96–1.16)	0.27	1.00 (0.99–1.01)	0.153	1.01 (1.01–1.02)	<0.001
180-day all-cause mortality												
Unadjusted	1.03 (0.99–1.06)	0.11	1.08 (1.02–1.31)	0.005	0.89 (0.84–0.95)	<0.001	0.96 (0.88–1.04)	0.28	1.00 (0.99–1.00)	0.42	1.01 (1.00–1.01)	0.18
Adjusted[a]	1.04 (1.01–1.07)	0.02	1.10 (1.05–1.17)	<0.001	0.91 (0.85–0.97)	0.004	0.95 (0.87–1.04)	0.25	1.00 (0.99–1.01)	0.92	1.01 (1.00–1.01)	0.032

Abbreviations: BUN, blood urea nitrogen; CCB, calcium channel blocker; CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LOS, length of stay; Na, sodium; RPP, rate pressure product; SBP, systolic blood pressure.

[a] Adjusted for age, BUN, baseline Na, baseline dyspnea, randomization to nesiritide, β-blockers, CCB, pacemaker, and ICD. N = 246 for 30-day outcomes; N = 315 for 180-day outcomes.

[b] Adjusted for above variables, plus baseline laboratory values (either heart rate, or SBP or RPP) and an indicator for LOS >10 days. N = 221 for 30-day outcomes; N = 298 for 180-day outcomes.

[c] Per 5-bpm increase.

[d] Per 10-mm Hg increase.

[e] Per 100 bpm × mm Hg increase.

patients with HFpEF, is associated with improved outcomes, as supported by prior studies.[20,40] These data provide a rationale for future studies to assess whether interventions to maintain or reduce heart rate during hospitalization improve outcomes.

With heart rate and SBP so intricately linked to one another, we assessed the product of both in the RPP to determine if this would be a useful measurement with regard to prognostic assessment. Baseline RPP was not associated with outcomes in either HFpEF or HFrEF patients. However, the change in RPP—an increase in RPP from baseline to discharge—was associated with increased 30-day mortality and HF rehospitalization in both HFpEF and HFrEF. Interestingly, this seems to be driven differently in each population; with HFpEF, RPP was driven by both heart rate and SBP, whereas in HFrEF, the prognostic utility of RPP was driven largely by heart rate, suggesting possible different pathophysiological mechanisms or adaptive physiology of HFpEF compared with HFrEF. Of note, we did not find any additional associative information with the baseline RPP variable as compared with baseline SBP and heart rate variables alone for both primary and secondary outcomes.

4.1 | Study limitations

This was a retrospective analysis and causal relationships cannot be determined. There were strict inclusion/exclusion criteria that may not apply to all HF patients. HFpEF was defined with an LVEF cutoff of 40%, and this definition varies in other studies. Information regarding heart rate and SBP was taken from documented single values that may not be representative of the longitudinal hemodynamic state of the patient and may be better captured by more data points. Furthermore, baseline vital signs were measured at time of enrollment, which may not have been consistent with heart rate and SBP at time of initial presentation with acute decompensated HF. In these circumstances, heart rate and SBP may not truly be representative of true "baseline" values, as these patients may have already been treated with medications or have had shifts in their hemodynamics by the time of enrollment. Our study focused on acute decompensated HF patients and may not be applicable to chronic HF patients. We did not find a significant difference between HFpEF and HFrEF based on interaction analyses; however the HFrEF population was significantly larger than the HFpEF population, and the analysis may have been underpowered.

5 | CONCLUSION

Our data describe the associations of clinical outcomes with heart rate and SBP in acute HF exacerbation, with a focus on patients with HFpEF. In general, patients with lower heart rate had more comorbidities and higher usage of therapies to control heart rate compared with patients with higher heart rate. Baseline SBP was associated with 180-day all-cause mortality in an inverse manner. Further, change in heart rate and SBP from baseline to discharge was associated with 30-day all-cause mortality or HF rehospitalization. These findings highlight potential benefits of monitoring the trend of vital signs

during hospitalization and suggest potential opportunities to target these parameters with therapies to improve outcomes.

Conflicts of interest

Robert J. Mentz receives research support from Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Novartis, Otsuka, and ResMed; and has received honoraria from HeartWare, Janssen, Luitpold Pharmaceuticals, Inc., Novartis, ResMed, and Thoratec/St. Jude. He has served on an advisory board for Luitpold Pharmaceuticals, Inc. The authors declare no other potential conflicts of interest.

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